REMARKS

Claims 6-8, 10-22, and 25-28 are pending in the instant application. No new matter has been added as a result of the above-described amendments. Support for the amendments can be found in the specification at, for example, page 17, lines 1-6. The rejections set forth in the Office Action are traversed by argument below.

1. Rejections of claims 6-8, 10-22, and 25-28 under 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 6-8, 10-22, and 25-28 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Action states that while claim 25, as amended in Applicants' response to the Office Action mailed August 14, 2001, is directed to a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2, or a KGF-2 protein consisting of residues 66 through 208 of the amino sequence set forth in SEQ ID NO: 2 and an N-terminal methionine, the as-filed specification does not disclose a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2. The Action also states that while Applicants indicate in their response to the Office Action mailed August 14, 2001 that the KGF-2 protein consisting of residues 66 through 208 of the amino sequence set forth in SEQ ID NO: 2 and the disclosed variant dN29 FGF-10 describe identical proteins, the specification discloses that Figure 2 depicts the amino acid sequence of dN29 FGF-10, which is identical to residues 69 through 208 – rather than 66 through 208 – of the amino sequence set forth in SEQ ID NO: 2.

Applicants respectfully disagree with the Action's assertion that the as-filed specification does not disclose a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2. Claim 25, as originally presented in Applicants' response filed September 11, 2000, recited a KGF-2 protein consisting of the amino acid sequence NH_2-His-Val-Arg-Ser-Tyr-[Asn^{71}-Ser^{208}]-COOH or the amino sequence NH_2-His-Val-Arg-Ser-Tyr-[Asn^{71}-Ser^{208}]-COOH also having an N-terminal methionine. As noted in the instant Action, Applicants amended claim 25 in their response to the Office Action mailed August 14, 2001 to replace the term "NH_2-His-Val-Arg-Ser-Tyr-[Asn^{71}-Ser^{208}]-COOH," which was inconsistent with 37 C.F.R. §§ 1.821(b) and

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(d) and 1.822(d), with the term "residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2," which is consistent with M.P.E.P. § 2423.03. Applicants contend that both terms describe the *same* KGF-2 variant.

Applicants first wish to direct the Examiner's attention to page 18, lines 6-8 of the specification, where Applicants teach a KGF-2 variant having the amino acid sequence NH_2-His-Val-Arg-Ser-Tyr-[Asn^{71}-Ser^{208}]-COOH. Applicants also note that the instant specification teaches that (a) Figure 1 and SEQ ID NO: 2 depict the full-length amino acid sequence of recombinant human KGF-2 (page 5, lines 25-26), (b) the initial 36 amino acid residues (*i.e.*, Met^{1} to Thr^{36}) of sequence depicted in Figure 1 and SEQ ID NO: 2 represent the putative leader sequence of full-length KGF-2 (page 5, lines 26-28), and (c) the term "[Asn^{71}-Pro^{203}]," for example, represents residues 71 through 203 of SEQ ID NO: 2 (page 15, lines 14-15). Exhibit A shows the amino acid sequence of SEQ ID NO: 2, with the putative leader sequence indicated by double-underlining, the residues at positions 66-70 (*i.e.*, His-Val-Arg-Ser-Tyr) indicated by bold underlining, and the residues at positions 71-208 (*i.e.*, [Asn^{71}-Ser^{208}]) indicated by underlining. Applicants contend that Exhibit A clearly illustrates that the terms "NH_2-His-Val-Arg-Ser-Tyr-[Asn^{71}-Ser^{208}]-COOH" and "residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2" are merely alternative expressions for the *same* amino acid sequence, and that the explicit recitation of the amino acid sequence NH_2-His-Val-Arg-Ser-Tyr-[Asn^{71}-Ser^{208}]-COOH in the as-filed specification provides support for a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2.

Applicants next address the Action's assertion that the disclosed variant dN29 FGF-10 and the KGF-2 protein consisting of residues 66 through 208 of the amino sequence set forth in SEQ ID NO: 2 do not describe identical proteins. Applicants agree that the variant described in Example 3 is dN29 hFGF10 rather than ΔN29 KGF-2, and therefore, the variant described in Example 3 consists of residues 69 through 208 of the amino sequence set forth in SEQ ID NO: 2 rather than residues 66 through 208. Applicants, however, contend that because the dN29 hFGF10 variant, which is three amino acids shorter than the ΔN29 KGF-2 variant, was found to exhibit proliferative activity in a Balb/MK mouse keratinocyte proliferation assay (*see* Example 2), one of ordinary skill in the art would expect the slightly longer ΔN29 KGF-2 variant to also exhibit the proliferative activity of

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mature KGF-2. Moreover, as Applicants noted in their response to the Office Action mailed August 14, 2001, the *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement* ("*Guidelines*") do not require that Applicants show an actual reduction to practice in cases such as this one. Rather, the *Guidelines* merely state that:

> [D]escribing an actual reduction to practice is one of a number of ways to show possession of the invention. ... Actual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps, in such a way as to distinguish the composition with particularity from all others.

Guidelines, 66 Fed. Reg. 1099, 1101 (2001). Applicants, therefore, respectfully submit that claims 6-8, 10-22, and 25-28 satisfy the requirements of 35 U.S.C. § 112, first paragraph, in that Applicants had possession of the claimed invention, and request that this ground of rejection be withdrawn.

The Office Action also asserts a rejection of claims 6-8, 10-22, and 25-28 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The Action states that because the specification as filed does not provide any guidance or working examples regarding a keratinocyte growth factor-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2, and the art is silent with respect to this protein, and because of the complex nature of the invention, and the unpredictability of mutation on protein structure and function, it would require undue experimentation for a skilled artisan to make and use the claimed invention.

Applicants understand that the underlying basis for this rejection is the Patent Office's belief that the claimed KGF-2 variant was not described in the as-filed specification. Applicants respectfully submit that they have traversed this misunderstanding in their response to the written description rejection set forth above, and further contend that, once the Patent Office appreciated Applicants' disclosure of the claimed variant, the Office will appreciate that the instant specification is enabling for the disclosed variant. In addition, and as discussed in Applicants' response to the Office Action mailed August 14, 2001, the instant specification teaches several pharmaceutically and physiologically acceptable vehicles that can be combined with the KGF-2 protein of the invention to

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form a suitable pharmaceutical composition (page 43, line 29 to page 46, line 21); procedures for determining acceptable dosages for use in administering the pharmaceutical compositions of the invention (page 47, line 10 to page 48, line 8); that because the KGF-2 proteins of the invention can be used, *inter alia*, to modulate epithelial cell proliferation in the gastrointestinal tract, the KGF-2 proteins of the invention are useful for treating or preventing diseases and disorders of the gastrointestinal tract (page 54, line 5 to page 61, line 4); that a pharmaceutical composition comprising the dN29 hFGF10 variant and a pharmaceutically acceptable vehicle is effective in preventing chemotherapy-induced pulmonary fibrosis in rats (Example 3), and that the dN29 hFGF10 variant retains KGF-2 activity in a murine keratinocyte proliferation assay (Example 2). Applicants contend, therefore, that in view of the teachings of the instant specification, one of ordinary skill in the art would know how to make and use the claimed invention. Applicants further contend that based on the teaching in the instant specification that a slightly shorter truncation KGF-2 variant retains KGF-2 activity in a murine keratinocyte proliferation assay, it would not require undue experimentation for a skilled artisan to make and use the claimed invention. Applicants, therefore, respectfully request that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, first paragraph, have been traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner Kemmerer believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Dated: September 19, 2003

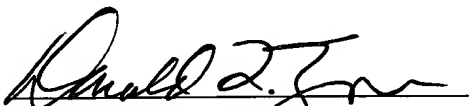
By: 
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EXHIBIT A

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Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu
 1               5                  10                  15

Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser
            20                  25                  30

Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu
        35                  40                  45

Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly
    50                  55                  60

Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg
65                  70                  75                  80

Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly
                85                  90                  95

Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu
            100                 105                 110

Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser
        115                 120                 125

Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys
    130                 135                 140

Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly
145                 150                 155                 160

Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met
                165                 170                 175

Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr
            180                 185                 190

Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
        195                 200                 205
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